Remarks

Applicants cancel pending claims 92-103, inclusive, and submit new Claims 104-121. Applicants respectfully request that the new claims be entered.

The new claims are supported throughout the specification of the application as filed and add no substantive new matter. Bases for new claims 104-107 are found in at least the following locations:

Claim	Basis
104-107	Example 13
108-111	Page 10, lines 7-10
112-115	Page 13, line 35 through page 14, line 5
116-119	Page 16, lines 16-20
120-123	Page 9, lines 14-19 and page 30, line 32 through page 31, line 4
124-127	Page 38, lines 28-30

According to Example 13 of the instant application (see pp. 72-73), "there is minimal dissociation of the heterodimer under various solution conditions after three month (sic) of incubation at room temperature or below." The data, shown in Table 1 below, indicate that the heterodimer content of an FSH formulation with benzyl alcohol remains about the same as the heterodimer content of a control FSH formulation without benzyl alcohol, when the formulations are stored at refrigerated conditions (4°C) or at room temperature (22°C). Additionally, these data show that the heterodimer content of the FSH formulation containing benzyl alcohol stored at room temperature does not significantly differ at a given time point from the heterodimer content of the same formulation stored at refrigerated conditions. These data are the bases for Claims 104-107, which provide a measure of the stability of the FSH formulation containing benzyl alcohol by comparison with a control FSH formulation lacking benzyl alcohol.

Table 1. Heterodimer stability of rFSH variant monitored by SE-HPLC.

Sample	% Dimer					
	1 month			3 months		
	4°C	22°C	37°C	4°C	22°C	37°C
20 µg/mL in PBS	100	100	88.9	100	100	77.3
20 µg/mL in PBS 3.15 µg/mL m-cresol	100	100	86.2	100	100	64.6
20 µg/mL in PBS 10 µg/mL benzyl alcohol	100	100	89.1	100	100	57.1
50 µg/mL in PBS	100	100	100	100	100	81.1
50 µg/mL in PBS 3.15 µg/mL m-cresol	100	100	90	100	100	75.7
50 µg/mL in PBS 10 µg/mL benzyl alcohol	100	100	87	100	100	61.0

To further demonstrate the stability of the preserved FSH solution formulations of the instant application, additional data are provided in the accompanying declaration of Dr. Ranmali D. Wijayaratne, attached. Those data buttress the data supplied in Example 13. Using a validated size exclusion method, Dr. Wijayaratne's declaration provides data that are more accurate, wherein the heterodimer content is not 100% at all time points for refrigerated and room temperature conditions. FSH variant formulations containing benzyl alcohol were compared with control formulations lacking benzyl alcohol. The differences in the heterodimer content between formulations with and without benzyl alcohol and the rates of loss of heterodimer content were compared. Additionally, rates of loss of heterodimer content in were compared for samples that were refrigerated and stored at room temperature. According to Dr. Wijayaratne, the experiment indicated that at refrigerated conditions and at room temperature the rate of heterodimer loss for the FSH formulations with and without benzyl alcohol were about the same. (Wijayaratne, ¶ 18, p. 4)

Reply Under 37 C.F.R. § 1.116

I. Status of the Claims

Claims 92-103 are cancelled, thereby obviating the rejections against them. Claims 104-113 have been added by amendment.

II. New Claims 104-113 Are Not Obvious Under 35 U.S.C. § 103(a)

A. The Rejection

The Examiner rejected previous claims Claim 92-95 under 35 U.S.C. § 103(a) as unpatentable over De Meere, *et al.* (U.S. Patent No. 5,384,132; "De Meere") in view of Buch-Rasmussen, *et al.* (U.S. Patent No. 5,945,187; "Buch-Rasmussen") and Bornstein, *et al.* (U.S. Patent No. 5,681,822; "Bornstein"). She further rejected previous claims Claim 96-103 under 35 U.S.C. § 103(a) using the same art in further view of Carey, *et al.* (US Patent No. 4,746,508; "Carey"). The Examiner alleged that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of various concentrations of recombinant human follicle stimulating hormone (FSH) taught by De Meere by using the teachings of benzyl alcohol regarding preserving, concentration, and solubilizations taught by Buch-Rasmussen and Bornstein" and "use the teachings of Carey, *et al.*" The Examiner further alleged, "The motivation and expected success is provided both by Buch-Rasmussen and Bornstein who teach longer storage of pharmaceutical compositions and antibacterial action using benzyl alcohol" and "by the use of sodium phosphate, which is taught as a physiologically acceptable carrier and offers buffering capacity that maintains the pH" (from Carey).

As Claims 92-103 have been cancelled, the rejections under § 103(a) are obviated. However, new Claims 104-113 have been added. The evidence and comments below demonstrate that the new claims are patentable over the cited art and obviate the Examiner's rejection.

B. The Scope of the Prior Art

The declaration of Dr. John M. Beals accompanying this response provides a thorough description scope of the prior art at the time of filing the instant application. According to Dr. Beals, numerous FSH products were marketed over a period of thirty years or more before the instant invention. However, none of the products contained a preservative. Thus, no multi-dose product was available, even though FSH therapy required multiple administrations to the patient. (Beals, ¶ 41, p. 9.)

None of the references cited by the Examiner disclose or suggest formulations of FSH and benzyl alcohol. De Meere teaches that a dicarboxylic acid stabilizer can be added to FSH to stabilize the protein, but De Meere's stabilization occurs in the lyophilized form; it does not occur in a solution formulation. Buch-Rasmussen

teaches that preservatives can be added to protein solutions (no mention of FSH) and improve shelf life. Buch-Rasmussen does not address stability of the protein, especially not heterodimer stability. Bornstein teaches that benzyl alcohol can be added to a nucleoside to solubilize and preserve the solution. Bornstein does not address the issue of protein stability. Combination of these three references would not suggest that one of skill in the art could combine FSH with benzyl alcohol to achieve a pharmaceutically acceptable formulation, particularly not a formulation that retains heterodimer content.

Contrary to the Examiner's assertion, the evidence provided herein clearly demonstrates that the skilled person was not motivated to combine the general teachings of preserved protein formulations with FSH.

In fact, the evidence demonstrates that human chorionic gonadotropin (hCG), a gonadotropin related in structure to FSH, was formulated as a preserved product for more than forty years prior to the instant invention. (Beals, ¶ 57, p. 12.) Moreover, many other protein products were available as multi-dose products with preservatives from the 1960's through the time of the instant invention. (Beals, ¶ 68, p. 15.)

C. Differences Between the Claimed Invention as a Whole and the Art

The claimed invention as a whole refers to a pharmaceutically acceptable formulation comprising FSH or FSH variant and benzyl alcohol. The art only contains references with FSH but no preservatives and references with other proteins or nucleosides in preserved solution formulations that contain no FSH. None of the prior art contains an FSH formulation preserved with benzyl alcohol.

D. Level of Ordinary Skill in the Art

The ordinarily skilled artisan in the field of protein solution formulations would know that multi-dose solution formulations existed prior to this invention for several protein products other than FSH. The art indicates that the interaction between a preservative and a protein in a formulation is a complex phenomenon that is highly dependent on the formulation characteristics including, but not limited to, the specific choice and concentration of preservatives, proteins, and other excipients such as buffers, stabilizers, and surfactants (*see, e.g.*, Lam *et al.*, *Pharm. Res.* 14(6): 725-29 (1997); Akers, *Pharm. Technol.* May: 36-46 (1984)). These characteristics "play a significant role in determining the extent of the interaction and consequently

the stability of the product." (Lam, *supra.*) Accordingly, the skilled artisan knows that achieving the optimum formulation requires experimentation with different combinations of protein, preservative, and excipients.

Also familiar with FSH and its well-known instability, the ordinarily skilled artisan would know that scientists have attempted to stabilize FSH formulations by formulating with dicarboxylic acids, formulating with saccharides, adding excess oxidizers like methionine, and forming single-chain FSH molecules:

> The stability of proteins in aqueous formulations is generally a problem in pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions. Usually therefore those preparations are stored in a dry form, as is obtained after lyophilization. A stabilized gonadotropin containing lyophilized pharmaceutical formulation is disclosed in European Patent No. 448,146 (Akzo N. V.). These preparations contain organic carboxylic acids, particularly citric acid, and optionally a non-reducing sugar such as sucrose. Another solid gonadotropin containing pharmaceutical composition comprising sucrose as a stabilizer is disclosed in the International Patent Application WO 93/11788 (AppliedResearch Systems ARS Holding N. V.).

(Skrabanja, U.S. Patent No. 5,929,028, col. 2, ll. 21-30). "It is known that highly purified proteins are time-unstable and are stabilized, for instance, in admixture with saccharides, such as lactose and mannitol or else with proteins and amino acids, such as albumin and glycine." (Samaritani, U.S. Patent No. 5,650,390, col. 1, ll. 19-22). "The single-chain forms of the heterodimers or homodimers have a number of advantages over their dimeric forms. . . . [T]hey are generally more stable." (Boime, U.S. Patent No. 6,238,890, col. 4, ll. 18-20). References such as these demonstrate the instability of FSH, especially in solution formulations. None of these efforts included benzyl alcohol.

E. Objective Evidence of Non-Obviousness

As an initial matter, the Applicants note that the Examiner has not provided evidence that one skilled in the art would be motivated to combine the references cited (i.e., De Meere, Buch-Rasmussen, and Bornstein). None of these references suggest combination of FSH with benzyl alcohol to yield a pharmaceutically acceptable formulation, preferably, one that is suitable for multi-dose or that would

yield a stable formulation. Nor does this art provide a reasonable expectation that combination would yield such a formulation.

To demonstrate that the claims in this amendment are not obvious, the Applicants assert three arguments. First, evidence provided by Dr. Beals demonstrates that FSH products were known in the art at least since the 1970's. (Beals, ¶ 9, pp. 2-3.) Preserved formulations of proteins other than FSH were also known in the art during that time period. (Beals, ¶¶ 57-60, pp. 12-13.) In fact, the same companies that developed and sold FSH products also developed and sold preserved formulations of other proteins. (Beals, ¶ 59, p. 12.) For example, Serono concurrently produced Pergonal, a non-preserved FSH product, and Profasi, a preserved, multi-dose human chorionic gonadotropin (hCG) product. (Beals, ¶ 15, p. 3.) Similarly, Organon concurrently produced Humegon, a non-preserved FSH product, and Pregnyl, a preserved, multi-dose hCG product. (Beals, ¶ 20, pp. 4-5.) If it were obvious to combine the FSH from one product with the preservative from another, it is likely that the skilled artisan would have combined them many years ago. Instead, a long gap (roughly 30 years) exists between the time when unpreserved FSH products and preserved formulations of other proteins were developed and first marketed and the time when a preserved, FSH formulation was conceived and reduced to practice. This gap in time evidences that the invention was not obvious.

Methods of treatment employing FSH typically require multiple injections of the protein formulation. Yet, until a time after the instant invention was filed, no multi-dose product was marketed. Several other protein products that required multiple injections over a series of days, such as human chorionic gonadotropin, insulin, and human growth hormone, were on the market during that timeframe. Each of these products contained a preserved diluent to allow for multiple dosing over several days from one container. On the other hand, FSH products had to be reconstituted daily, and any of the expensive FSH solution that remained at the end of the day had to be discarded. Unfortunately, although the need for a preserved FSH product existed, no product was developed until decades after single dose FSH was marketed. (Beals, ¶ 76, p. 16). This long-felt but unresolved need is further evidence of non-obviousness.

The long-felt need, coupled with the long gap in time to develop an FSH formulation preserved with benzyl alcohol, indicates that there was no motivation to combine FSH with benzyl alcohol and more likely that there was skepticism that

deterred the skilled man from even trying. (Beals, ¶ 72, p. 16.) Regardless, this long gap in time to develop a FSH formulation containing benzyl alcohol for pharmaceutical use demonstrates that the formulation was not obvious to formulators at the time of the instant invention.

Second, although both FSH and benzyl alcohol were known in the art prior to this invention, compatibility of the excipients (that is, would a formulation of FSH and benzyl alcohol be unstable and therefore not be viable as a pharmaceutical product) was not predictable from the art. Even if FSH and benzyl alcohol were combined, the ordinarily skilled artisan would have known that extensive experimentation would be required to determine whether the formulation would be suitable for use as a pharmaceutical, let alone a multi-dose pharmaceutical. For the instant invention, stability of the preserved formulation was measured by the rate of heterodimer loss over time compared to the rate of heterodimer loss in a control formulation lacking benzyl alcohol. The fact that the rate of heterodimer loss over time is about the same in formulations with and without benzyl alcohol, at both refrigerated conditions and room temperature, was not predictable. (Wijayaratne, ¶ 21, p. 4.)

Third, if one skilled in the art were to speculate regarding compatibilities of FSH and benzyl alcohol he would have inspected the art regarding preservatives like benzyl alcohol, m-cresol, and phenol to see what effect they might have on a formulation. The art indicates that these preservatives tend to destabilize protein formulations. (*See, e.g.*, Maa & Hsu, *Intl. J. Pharm.* 140:155-68 (1996); Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998); Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997); Lam, *supra*). More likely than not, he would have expected that benzyl alcohol would destabilize the preserved formulation when compared to the control formulation, especially as temperature increased from refrigerated conditions to room temperature. (Wijayaratne, ¶ 21, p. 4.) However, as demonstrated in Example 13 of the instant application and the Declaration of Dr. Wijayaratne, the rate of heterodimer loss was about the same with benzyl alcohol as without it, at both room temperature and at refrigerated conditions. (Wijayaratne, ¶ 18, p. 4.) These results are unexpected.

Considering the long-felt need for preserved FSH formulations for multi-dose use, the fact that FSH had only been provided in lyophilized forms and was considered unstable, and the concurrent and extensive availability of preserved multi-dose hCG and other protein products, it is evident that a person of ordinary skill

in the art was not motivated to combine the references cited by the Examiner.

The Applicants assert that the objective evidence described above indicates that the new claims, added through this amendment, are not obvious. The Applicants respectfully request that the Examiner enter these claims and advance the application to allowance.

IV. Conclusions

In view of the remarks and amendments provided herein, the Applicants respectfully submit that all rejections have been obviated through cancellation of the claims. The Applicants respectfully request entry of the amendments, consideration of the arguments and evidence presented herein, and allowance of all claims.

The Applicants urge the Examiner to call the Applicants' agent at (317) 433-3422 if a telephone conversation or office interview would be helpful in expediting the prosecution of this case.

Respectfully submitted,

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February 18, 2003

Revised Claims for 09/928,198 (X-12383N) After Amendment

We claim:

104. (New) A pharmaceutically acceptable formulation comprising FSH or FSH variant and benzyl alcohol in an aqueous diluent.

105. (New) A pharmaceutically acceptable formulation suitable for multi-dose comprising FSH or FSH variant and benzyl alcohol in an aqueous diluent.

106. (New) A pharmaceutically acceptable formulation comprising FSH or FSH variant and benzyl alcohol in an aqueous diluent, wherein the heterodimer content is sufficiently stable to provide a multi-dose pharmaceutical product.

107. (New) A pharmaceutically acceptable formulation comprising FSH or FSH variant and benzyl alcohol in an aqueous diluent, wherein the rate of heterodimer loss at room temperature is about the same in the formulation as in a control formulation lacking benzyl alcohol.

108. (New) The formulation of Claim 104, wherein the FSH is human FSH.

109. (New) The formulation of Claim 105, wherein the FSH is human FSH.

110. (New) The formulation of Claim 106, wherein the FSH is human FSH.

111. (New) The formulation of Claim 107, wherein the FSH is human FSH.

112. (New) The formulation of Claim 104 comprising an FSH variant of the formula:

α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSEST
CCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

ß-subunit: (SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKELV
YETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE.

113. (New) The formulation of Claim 105 comprising an FSH variant of the formula:

α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSEST
CCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

ß-subunit: (SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKELV
YETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE.

114. (New) The formulation of Claim 106 comprising an FSH variant of the formula:

α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSEST
CCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
ß-subunit: (SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKELV
YETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE.

115. (New) The formulation of Claim 107 comprising an FSH variant of the formula:

α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSEST
CCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
ß-subunit: (SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKELV
YETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE.

116. (New) The formulation one of Claim 104, wherein the FSH or FSH variant is urinary FSH.

117. (New) The formulation one of Claim 105, wherein the FSH or FSH variant is urinary FSH.

118. (New) The formulation one of Claim 106, wherein the FSH or FSH variant is urinary FSH.

119. (New) The formulation one of Claim 107, wherein the FSH or FSH variant is urinary FSH.

120. (New) The formulation of Claim 104, wherein the FSH or FSH variant is produced through the use of recombinant DNA technology.

121. (New) The formulation of Claim 105, wherein the FSH or FSH variant is produced through the use of recombinant DNA technology.

122. (New) The formulation of Claim 106, wherein the FSH or FSH variant is produced through the use of recombinant DNA technology.

123. (New) The formulation of Claim 107, wherein the FSH or FSH variant is produced through the use of recombinant DNA technology.

124. (New) The formulation of Claims 104, wherein the FSH or FSH variant is at a concentration of 50 μg/mL to about 200 μg/mL.

125. (New) The formulation of Claims 105, wherein the FSH or FSH variant is at a concentration of 50 μg/mL to about 200 μg/mL.

126. (New) The formulation of Claims 106, wherein the FSH or FSH variant is at a concentration of 50 μg/mL to about 200 μg/mL.

127. (New) The formulation of Claims 107, wherein the FSH or FSH variant is at a concentration of 50 μg/mL to about 200 μg/mL.